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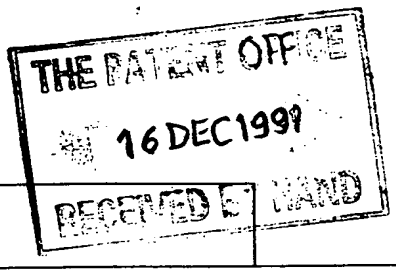

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MBUS 1129

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Form 1/77

Patents Act 1977

❶ Title of invention

1 Please give the title of the invention

IMPROVEMENTS IN CHEMICAL COMPOUNDS

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❷ Do not give trading styles, for example, 'Trading as XYZ company', nationality or former names, for example, 'formerly (known as) ABC Ltd' as these are not required.

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Country *(and State of incorporation, if appropriate)* GB

2b If you are applying as an individual or one of a partnership please give in full:

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Agent's name I C WISHART

Agent's address

JOHNSON MATTHEY TECHNOLOGY CENTRE
BLOUNTS COURT, SONNING COMMON,
READING

Postcode RG4 9NH

Agent's ADP number N2 7 2 7 1 2 0 0 1 JG.

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Continuation sheets for this Patents Form 1/77	NIL		
Claim(s)	5	Description	18
Abstract	1	Drawing(s)	NIL

8b Which of the following documents also accompanies the application?

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Priority documents *(please state how many)*	
Translation(s) of Priority documents *(please state how many)*	
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⑤ Claiming an earlier application date

5 Are you claiming that this application be treated as having been filed on the date of filing of an earlier application?

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MBUS 1129

IMPROVEMENTS IN CHEMICAL COMPOUNDS

This invention concerns improvements in chemical compounds, more especially it concerns compounds and pharmaceutical compositions. In particular it concerns compositions and compounds having activity in *in vitro* tests on Human Immunodeficiency Virus-infected cells.

The disease known as Acquired Immune Deficiency Syndrome (AIDS) caused by infection by HIV has attracted immense research effort because of the effects of the disease on infected individuals and the dangers of the disease spreading to a wider section of the population. In general, although various chemo-therapeutic treatments have been advocated, and some compounds have emerged as a potential basis for treatment, there is still a need for alternatives. In particular, most treatments such as the compound known as AZT have a high toxicity to

cells, and it would be desirable to find compounds which are less toxic. In man, the development of resistance to AZT has been identifi as additional clinical problem.

We have found a group of compounds which show protective properties in <u>in vitro</u> screens of cells challenged with HIV-1 and/or HIV-2, and are therefore indicated as having potential for the treatment of AIDS and AIDS Related Complex and other viral and especially retroviral infections. Accordingly, the present invention provides the use of compounds defined below, in pharmaceutical compositions for treating HIV-infected patients. The invention further provides pharmaceutical compositions comprising a said compound in combination or association with a pharmaceutically acceptable diluent or excipient, for the treatment of HIV-infected patients. The invention may also be defined as the use of a said compound for the manufacture of a medicament for the treatment of HIV-infected patients. The invention further provides a process for the production of a pharmaceutical composition for the treatment of a HIV-infected patient, comprising the combination of a compound as defined below with a pharmaceutically acceptable diluent or excipient, and formulating said composition into a form suitable for administration to said patient. The invention also provides a method of treatment of an HIV-infected patient, comprising administering to said patient an effective dose of a said compound. It is to be understood that treatment includes prophylactic treatment of patients at risk, in view of the protective properties observed. Whilst this description is especially directed to combating HIV, this invention includes other aspects in which other diseases may be treated, including for example microbial infections.

A 2,2′-dimer of cyclam has been reported as being isolated as a 2% by-product in the synthesis of cyclam (1,4,8,11-tetraaza-cyclotetradecane) (Barefield et al, J C S Chem Comm (1981), 302). This compound was stated to be insoluble in water. We believe that the insoluble 2,2′-bicyclam is a mixture of the 2R,2′R and 2S,2′S enantiomers; we have characterised a soluble dimer which we believe to be the meso 2R,2′S isomer. The 6,6′-bicyclam isomer has been reported by Fabbrizzi et al, Inorg Chem 25, 2671 (1986). Certain N,N′-linked bicyclic compounds have been reported by Ciampolini et al, Inorg Chem 26, 3527 (1987). No biological activity has been suggested for such compounds.

US Patent 4,156,683 discloses monocyclic and bicyclic macrocyclic compounds, which are said to have biological activity in regulating sodium, potassium and calcium levels in mammals. Additionally, a specific group of N-alkylated monocyclic compounds are said to possess activity against A_2 influenza viruses in a modified Hermann test on chick fibroblast tissue. It is also said that the preferred compounds, which form complexes of greater stability, are those having three bridging chains between bridgehead nitrogen atoms, that is fused bicyclic compounds.

Our USP 5,021,409 describes linked cyclic compounds as being active against HIV-1 and HIV-2 in in vitro tests. We have now discovered that certain of these linked cyclic compounds exhibit surprisingly improved activity against HIV. Thus, the present invention concerns a selected group of the compounds taught in said USP, having activity of

at least an order of magnitude greater than the compounds tested in said USP.

The present invention provides as active compounds linked cyclic compounds of the general formula I

$$Z - R - A - R' - Y \qquad (I)$$

in which Z and Y are independently cyclic polyamine moieties having from 9 to 32 ring members and from 3 to 8 amine nitrogens in the ring spaced by 2 or more carbon atoms from each other,

A is an aromatic or heteroaromatic moiety, and

R and R′ are each a substituted or unsubstituted alkylene chain or heteroatom-containing chain which spaces the cyclic polyamines and the moiety A. The invention also encompasses acid addition salts and metal complexes of the compounds of formula I.

In the above formula, the cyclic polyamine moieties may be substituted or unsubstituted, and suitable substituents are alkyl and/or aryl groups, eg of up to 10 carbon atoms, and any other atoms or groups which do not substantially adversely affect the activity or toxicity of the compounds. Preferred moieties are those of 9 to 30 ring members, especially 9 to 20 ring members, most preferably 10 to 15 ring members, and preferred numbers of amine nitrogen atoms are 3 to 6. The moieties may be linked by attachment to the carbon atoms or nitrogen atoms of the polyamine ring, ie C-C′, C-N′, N-N′; preferably, the moieties are linked at nitrogen atoms. Y and Z may be identical or non-identical, although it is convenient that they are identical.

The aromatic or heteroaromatic moiety A tethers Y and Z through the linking groups R and R'. Moiety A may be phenyl or fused aromatic, heterocyclic or fused heterocyclic or joined aromatic, or joined heteroaromatic for example biphenyl or bipyridyl respectively. The moieties A may also be substituted at single or multiple non-linking positions with electron-donating groups, eg alkyl, thio, thioalkyl, hydroxyl, alkoxyl, amino and derivatives thereof, or electron-withdrawing groups or atoms, eg nitro, halogen, carboxy, arboxamido, sulfonic acid and derivatives thereof.

The linking group R may contain heteroatoms, eg O, N or S, and may be saturated, unsaturated or polyunsaturated, and is preferably alkyl or cycloalkyl of 1 to 12 carbon atoms, more preferably alkyl of 1 to 6 carbon atoms.

The invention also includes what may be termed "pro-drugs", that is protected forms of the linked cyclic compounds, which release the compound after administration to a patient. For example, the compound may carry a protective group which is split off by hydrolysis in body fluids, eg in the bloodstream, thus releasing active compound. A discussion of pro-drugs may be found in "Smith and Williams' Introduction to the Principles of Drug Design", H J Smith, Wright, 2nd Edition, London 1988.

A few of the active compounds according to the invention are known, (Inorg Chem 26 (1987), p 3527-3533 and J Chem Soc, Chem Commun, (1991), 206, 207).

Accordingly, certain of the compounds of formula I a· 'el. The invention accordingly provides novel linked cyclic po.,amine compounds of general formula Ia,

$$Z - R - A' - R' - Y \qquad \text{(Ia)}$$

in which Z, Y, R and R′ are as defined above, with R and R′ linked to nitrogen atoms in Z and Y, and

A′ is an aromatic or heteroaromatic moiety which is unsubstituted or substituted, provided that A′ is not unsubstituted phenylene when Z and Y are 14-membered tetraaza rings, and R and R′ are both methylene,

and their acid addition salts and metal complexes.

The invention further provides a method for the production of the compounds of formula Ia, which method comprises nucleophilic attack by cyclic polyamines Z′ and Y′ each having a single unprotected ring amine nitrogen, all other ring amine nitrogens being protected, on a compound of formula II

$$X - R - A' - R' - X \qquad \text{II}$$

wherein R, R′ and A′ are as defined above, and

each X is an active substituent which can be displaced by the unprotected amine nitrogens of polyamines Z′ and Y′ and is preferably selected from Br, Cl, I, methanesulfonate, 4-tolylsulfonate and trifluoromethane sulfonate,

and subsequently deprotecting the ring amine nitrogens.

It is well within the capabilities and knowledge of the skilled synthetic chemist to protect the amine nitrogens of cyclic polyamines, and it is preferred to use substitution by methanesulfonyl and/or 4-tolylsulfonyl and/or diethylphosphoryl. The compounds of formula II are known.

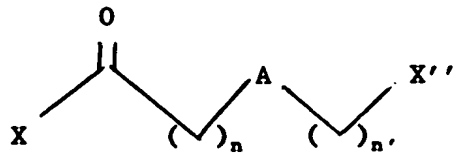
The reaction is preferably carried out in a solvent, such as acetonitrile or dimethylformamide, tetrahydrofuran or dioxane and in the presence of a base, for example sodium carbonate or potassium carbonate. The reaction generally takes place readily at room temperature to elevated temperature, to give a linked molecule having protected amine nitrogen atoms. In general, a mixture of products will be obtained, and we have found that chromatography on silica gel is a particularly convenient method of separation.

The deprotection step is suitably carried out by refluxing the protected molecule in a mixture of aqueous HBr and acetic acid or in the case of diethylphosphoryl in the presence of hydrogen chloride (gas) in THF or dioxane.

It is convenient that Z and Y are identical, so that the compound of formula II is reacted with two equivalents of the protected polyamine.

In the case where Z and Y are not identical, it is appropriate to modify the process described above, using as reactant a compound of

formula IIa,



IIa

in which A is is as defined above,

X′ is a halogen, preferably bromine or chlorine

X′′ is a halogen, preferably bromine or iodine, or tosyl or mesyl, and

n = 0 or a positive integer such as to yield chain R in the product, and

n′ = a positive integer such as to yield chain R′ in the product,

and reacting firstly with a protected cyclic polyamine Z′ and secondly reacting the reaction product with a protected cyclic polyamine Y′, subsequently reducing the carbonyl group on the chain, and thereafter deprotecting the ring amine nitrogens.

The first stage reaction is conveniently carried out in a solvent, for example triethylamine, and the second stage reaction is conveniently carried out under the conditions described above, that is in a solvent and in the presence of a base. Before deprotection, which may be accomplished as described above, it is necessary to reduce the carbonyl group on the linking chain using a reducing agent such as borane or lithium aluminium hydride, in manner generally known. The skilled synthetic chemist will be able to carry into effect the process of the

invention in its various stages and possible variants.

The compounds are indicated for the treatment of viral infections, especially retrovirus infections and particularly HIV infections, and the compounds of formula I are to be considered as active compounds for the pharmaceutical compositions, processes for making the same and methods of treatment mentioned above. In these aspects of the invention, it is to be understood that meso forms, enantiomers and resolved optically active forms of the compounds of formula I are included. Also, it is to be considered within the invention, compounds of formula I diluted with non-toxic or other active substances. Acid addition salts, for example hydrochlorides, and non-toxic labile metal complexes of the compounds of formula I are also active compounds according to the present invention. Non-toxic in the present context has to be considered with reference to the prognosis for the infected patient without treatment. Zinc and nickel complexes may be considered, whereas less labile metal atoms such as cobalt and rhodium are less preferred because of likely lower selectivity.

The present invention will now be illustrated by the following preparative examples.

EXAMPLE 1

a) 2,3,5,6-Tetrafluoro-p-xylene-α,α'-diol

To a stirred solution of perfluoroterephthalic acid (1.0g, 4.2mmol) in anhydrous THF (10ml) under an atmosphere of dry argon was added Borane. THF complex (1.0M solution in THF, 10 equivalents, 42ml)

dropwise, and the mixture stirred at room temperature overnight. The solution was evaporated under reduced pressure to give a colou· oil and the excess Borane destroyed by addition of anhydrous methanol (40ml) and evaporation (repeated three times). The residue was treated with 5% aqueous hydrochloric acid then the pH of the mixture was adjusted to pH9 with 1N aqueous sodium hydroxide solution and extracted with dichloromethane (3 x 50ml). The combined organic extracts were dried ($MgSO_4$) and evaporated to give 2,3,5,6-tetra-fluoro-p-xylene-α,α'-diol (0.75 g, 86%) as a white solid. This was used without further purification.

b) 2,3,5,6-Tetrafluoro-p-xylene-α,α'-diol dimesylate

To a stirred solution of 2,3,5,6-tetrafluoro-p-xylene- α,α'-diol (0.72g, 3.4mmol) in dichloromethane (40ml) containing triethylamine (1.2ml, 2.5 equivalents) was added methanesulfonyl chloride (0.58ml, 2.2 equivalents) dropwise at 0°C and the mixture was allowed to warm to room temperature overnight. The solution was washed with saturated aqueous sodium bicarbonate solution (2 x 20ml) and brine (2x 20ml) then dried ($MgSO_4$) and evaporated under reduced pressure. The residue was suspended in ether and filtered giving 2,3,5,6-tetrafluoro-p-xylene-α,α'-diol dimesylate (0.9g, 72%) as a white solid.

c) 1,1'-[2,3,5,6-Tetrafluoro-1,4-phenylenebis-(methylene)] -bis-tris(p-toluenesulfonyl)-1,4,8,11-tetraazacyclotetradecane

2,3,5,6-Tetrafluoro-p-xylene-α,α'-diol dimesylate (150mg, 0.4mmol), tris-(p-toluenesulfonyl)-1,4,8,11-tetraazacyclotetradecane

monohydrate 826mg, 1.2mmol, 3.0 equivalents) and potassium carbonate (252mg, 3.0 equivalents) in anhydrous acetonitrile (20ml) were heated to reflux with stirring under argon for 48 hours until all the dimesylate starting material had been consumed; confirmed by TLC (silica gel, 2% methanol in dichloromethane as eluent). The mixture was evaporated under reduced pressure and the residue was dissolved in ethyl acetate (40ml) and washed with saturated aqueous sodium bicarbonate solution (2 x 20ml) and brine (2 x 20ml) then dried ($MgSO_4$) and evaporated. The residue was purified by column chromatography on silica gel eluting with 2% methanol in dichloromethane giving a white foam identified by ^1H NMR and FAB-MS as 1,1'-[2,3,5,6-tetrafluoro-1,4-phenylenebis-(methylene)]-bis-tris-(p-toluenesulfonyl)-1,4,8,11-tetraazacyclotetradecane.
$C_{70}H_{86}N_8O_{12}S_6F_4$ requires C, 56.05; H, 5.78; N, 7.47; found C, 55.81; H, 5.73; N, 7.36.

d) 1,1'-[2,3,5,6-Tetrafluoro-1,4-phenylenebis-(methylene)]-bis-1,4,8,11-tetraazacyclotetradecane

1,1'-[2,3,5,6-Tetrafluoro-1,4-phenylenebis-(methylene)]-bis-tris-(p-toluenesulfonyl)-1,4,8,11-tetraazacyclotetradecane (200mg, 0.13mmol) was dissolved in a mixture of acetic acid and hydrobromic acid (48%) in a ratio of approximately 3:2 by volume (10ml) and heated to 100 C for 24 hours during which time a white solid precipitated. The mixture was allowed to cool and the solid was filtered off and washed with acetic acid and ether and dried <u>in vacuo</u> giving a white solid identified by ^1H NMR, FAB-MS and elemental analysis as 1,1'-[2,-3,5,6-tetrafluoro-1,4-phenylene-bis-(methylene)]-bis-1,4,8,11-tetraazacyclotetradecane octahydrobromide dihydrate (65 mg, 40%).

$C_{28}H_{62}N_8O_2Br_8F_4$ requires C, 26.73; H, 4.96; N, 8.90; found C, 26.84; H, 5.05; N, 8.21.

The following compounds were prepared using analogous methods to those described above in steps b)-d):

5-Nitro-m-xylene-α,α'-diol gave 1,1-[5-Nitro-1,3- phenylene-bis-(methylene)]-bis-1,4,8,11-tetraazacyclotetradecane octahydrobromide dihydrate.

$C_{28}H_{65}N_9O_4Br_8$ requires C, 27.31; H, 5.31; N, 10.24; found C, 27.49; H, 5.26; N, 9.75.

2,4,5,6-Tetrachloro-m-xylene-α,α'-diol gave 1,1'-[2,4,5,6-tetra-chloro-1,3-phenylene-bis-(methylene)]-bis-1,4,8,11-tetraaza-cyclotetradecane octahydrobromide dihydrate.

$C_{28}H_{62}N_8O_2Cl_4Br_8$ requires C, 25.40; H, 4.71; N, 8.46; found C, 25.72; H, 4.76; N, 8.05.

EXAMPLE 2

a) α,α'-Dibromo-1,4-dimethylnaphthalene

To a solution of 1,4-dimethylnaphthalene (0.5g, 3.2mmol) and benzoyl peroxide (0.08 equivalents, 62mg) in carbon tetrachloride (20ml) was added N-bromosuccinimide (1.14g, 2.0 equivalents) and the mixture was heated to reflux for 24 hours during which time a white solid precipitated. The mixture was filtered hot (to remove the succinimide by-product) and then allowed to cool over several hours during which time

a white cystalline solid precipitated. The solid was filtered off and dried giving 1,4-dimethylnaphthalene-α,α'- dibromide (473mg, 50%).

The following compound was prepared using methods analogous to steps c) and d) of Example 1:

1,4-Dimethylnaphthalene-α,α'-dibromide gave 1,1'-[1,4-naphthylenebis-(methylene)]-bis-1,4,8,11-tetraazacyclotetradecane octahydrobromide tetrahydrate.

$C_{32}H_{72}N_8O_4Br_8$ requires C, 30.20; H, 5.69; N, 8.81; found C, 30.28; H, 5.52; N, 8.66.

Example 3

a) 1-Benzyl-5,13-di-(p-toluenesulfonyl)-9-methanesulfonyl-1,5,9,13-tetraazacyclohexadecane.

To a solution of N,N-bis-[3-(p-toluenesulfonylamido-propyl)]benzylamine hydrochloride (25g) (NL Patent 6603655) in dry DMF (800ml) under argon was added sodium hydride (10 equivalents) in small portions over 3 hours. When the addition was complete the solution was heated at 60°C for 1 hour then allowed to cool and the excess sodium hydride was removed by filtration under argon. The filtrate was transferred to another dry flask and the solution was then heated to 100-110°C and bis-propanolamine- trimethanesulfonate [P Moore, J Chem Soc Dalton Trans 1985 (7) 1361-1364] (1.0 equivalent) in DMF (500ml) was added dropwise over 8 hours with rapid stirring. The temperature was maintained at 100-110 C for a further 16 hours, allowed to cool, then poured into iced water (1500ml) and the resulting off-white precipitate

that formed was collected by filtration. The solid was dissolved in dichloromethane (250ml) and the solution was washed with wat x 50ml), then dried ($MgSO_4$) and evaporated under reduced pressure to give a yellow oil. Trituration with ethanol (200ml) gave a white crystalline solid which was filtered off, washed with a small volume of ethanol, then ether and dried <u>in vacuo</u> to give 1-benzyl-5,-13-di-(p-toluenesulphonyl)-9-methanesulphonyl--1,5,9,-13tetraazacyclo-hexadecane (45%), identified by ^1H NMR and FAB-MS.

b) 1,9-Di-(p-toluenesulfonyl)-5-methanesulfonyl-1,5,9,13-tetraazacyclohexadecane.

To a solution of 1-benzyl-5,13-di-(p-toluene-sulfonyl)-9-methanesulfonyl-1,5,9,13-tetraazacyclohexadecane in formic acid (20ml) was added Palladium hydroxide on carbon (Pearlmans catalyst, 4.0g) and the resulting suspension was heated to reflux for 72 hours with stirring. The mixture was allowed to cool, then filtered through celite and the filtrate was evaporated under reduced pressure. The colourless oil which remained was dissolved in dichloromethane (50ml) and washed with 10% aqueous sodium hydroxide solution (2 x 20ml), and water (2 x 20ml) then dried ($MgSO_4$) and evaporated under reduced pressure. The residue was purified by column chromatography on silica gel eluting with 3% methanol in dichloromethane giving a white solid identified by ^1H NMR and FAB-MS as 1,9-di-(p-toluene-sulphonyl-5-methanesulfonyl-1,5,9,13-tetraazacyclohexadecane.

The mono-deprotected tetraazacyclohexadecane macrocycle described in step b) was used as described in Example 1 steps c) and d),

to prepare tetraazacyclohexadecane dimers.

The following compounds were prepared in this manner.

α,α'-Dibromo-m-xylene gave 1,1'-[1,3-phenylene-bis-(methylene)]-bis-1,5,9,13-tetraazacyclohexadecane octahydrobromide hexahydrate.

$C_{32}H_{76}N_8O_6Br_8$ requires C, 29.29; H, 6.15; N; 8.54; found C, 29.37; H, 5.50; N, 7.90.

α,α'-Dibromo-p-xylene gave 1,1'-[1,4-phenylene-bis-(methylene)]-bis-1,5,9,13-tetraazacyclohexadecane octahydrobromide hexahydrate.

$C_{32}H_{76}N_8O_6Br_8$ requires C, 29.29; H, 6.15; N, 8.54; found. C, 28.96; H, 5,47; N,7.96.

Other compounds which may be made according to the invention are:

1,1'-[1,3-phenylenebis(methylene)]-bis-1,5,9,13-tetraazacyclo-hexadecane

1,1'-[1,3-phenylenebis(methylene)]-bis-1,4,7-triazacyclododecane

1,1'-[1,4-phenylenebis(methylene)]-bis-1,4,7,triazacyclododecane

The compounds of the invention were tested in a screen by the MTT method (J Virol Methods 120: 309-321 [1988]). MT-4 cells (2.5 x 10^4/well) were challenged with HIV-1 (HTLV-IIIB) or HIV-2 (LAV-2 ROD) at a concentration of 100 $CCID_{50}$ and incubated in the presence of various concentrations of the test compounds, which were added immediately after

challenge with the virus. After 5 days culture at 37°C in a CO_2 incubator, the number of viable cells was assessed by MTT (tetrazolium) method. Antiviral activity and cytotoxicity of the compounds are expressed in the table below as IC_{50} (ug/ml) and CC_{50} (µg/ml), respectively. The potential therapeutic usefulness was assessed by calculating a Selectivity Index (SI) corresponding to the ratio of CC_{50} to IC_{50}. A control test was performed using the known anti-HIV treatment AZT.

In the table below, the compounds screened were:

AZT : known anti-HIV compound

A : 1,1'-[1,3-phenylenebis(methylene)]bis-1,4,8,11-tetraazacyclotetradecane

B : 1,1'-[1,4-phenylenebis(methylene)]bis-1,4,8,11-tetraazacyclotetradecane

C : 1,1'-[5-nitro-1,3-phenylenebis-(methylene)]-bis-1,4,8,11-tetraazacyclotetradecane

D : 1,1'-[2,3,5,6-tetrafluoro-1,3-phenylene-bis-(methylene)]bis-1,4,8,11-tetraazacyclotetradecane

E : 1,1'-[1,4-naphthylenebis(methane)]bis-1,4,8,11-tetraazacyclotetradecane

TABLE

Compound	Virus	IC_{50} (µg/ml)	CC_{50} (µg/ml)	SI
AZT (Comparison)	HIV-1	<0.008	> 1	> 125
A	HIV-1	0.03	>500	16,667
	HIV-2	<0.01	>500	>50,000
B	HIV-1	0.006	>500	83,333
	HIV-2	<0.01	>500	>50,000
C	HIV-1	0.05	55	1100
	HIV-2	0.07	55	756
D	HIV-1	0.01	60	6,000
	HIV-2	0.01	60	6,000
E	HIV-1	0.07	71	1,014
	HIV-2	0.05	71	1,420

It can readily be seen that the compounds according to the invention are highly active against HIV-1 and -2, with low toxicity, in the in vitro tests used.

Additional in vitro testing was carried out in view of the exceptional results in respect of compounds A and B. Both compounds were tested against three strains of Simian Immunodeficiency Virus (SIV), in MT-4 and MOLT-4 cells, and were found to exhibit IC_{50} values in excess of 100µg/ml. Thus, compounds according to the invention which are highly active against both forms of HIV were surprisingly essentially inactive against SIV, which many researchers had considered to be closely related to HIV. There are also indications that compounds A and B inhibit synctium formation between persistently (HIV-1)-or(HIV-2)-infected HUT-

78 cells and uninfected MOLT-4 cells, although at dosage levels about 2 orders of magnitude greater than the IC_{50} levels in the above ibed tests.

The pharmaceutical compositions of the present invention may be formulated according to well-known principles, and may desirably be in the form of unit dosages determined in accordance with conventional pharmacological methods. The unit dosage forms may provide a daily dosage of active compound in a single dose or in a number of smaller doses. Dosage ranges may be established using conventional pharmacological methods and are expected to lie in the range 1 to 50mg/kg of body weight. Other active compounds may be used in the compositions or administered separately, or supplemental therapy may be included in a course of treatment for a patient. The pharmaceutical compositions may desirably be in the form of solutions or suspensions for injection, in capsule, tablet, dragee or other solid form, or a liquid form such as a syrup, for oral administration. Suitable carriers and diluents are well known in the art, and the compositions may include excipients and other components such as taste-modifying agents to provide easier or more effective administration.

CLAIMS

1. A pharmaceutical composition comprising as active ingredient a linked cyclic compound of general formula I,

$$Z - R - A - R' - Y \qquad (I)$$

in which Z and Y are independently cyclic polyamine moieties having from 9 to 32 ring members and from 3 to 8 amine nitrogens in the ring spaced by 2 or more carbon atoms from each other,

A is an aromatic or heteroaromatic moiety,

R and R′ are each a substituted or unsubstituted alkylene chain or heteroatom containing chain,

or an acid addition salt or metal complex thereof, in admixture or association with a pharmaceutically acceptable diluent or carrier.

2. A composition according to claim 1, wherein, in the compound of formula I, R and R′ are linked to nitrogen atoms in Z and inY.

3. A composition according to claim 1 or 2, wherein, in the compound of formula I, each moiety Z and Y has 9 to 30 ring members.

4. A composition according to claim 3, wherein, in the compound of formula I, each moiety Z and Y has 10 to 15 ring members.

5. A composition according to any one of claims 1 to 4, wherein, in the compound of formula I, each moiety Z and Y has 3 to nine nitrogens.

6. A composition according to any one of claims 1 to 5, wherein, in the compound of formula I, R and R′ are methylene.

7. A composition according to claim 1, wherein the active ingredient is 1,1′-[1,3-phenylenebis (methylene)]-bis-1,4,8,11-tetra-azacyclotetradecane.

8. A composition according to claim 1, wherein the active ingredient is 1,1′-[1,4-phenylenebis(methylene)]-bis-1,4,8,11-tetra-azacyclotetradecane.

9. A composition according to any one of the preceding claims, in unit dosage form.

10. A linked cyclic compound of formula Ia,

$$Z - R - A' - R' - Y \qquad (Ia)$$

wherein Z, Y, R and R′ are as defined in claim 1, with R and R′ linked to nitrogen atoms in Z and Y, and A′ is an aromatic or heteroaromatic moiety which is unsubstituted or substituted, provided that A′ is not unsubstituted phenylene when Z and Y are 14-membered tetraaza rings, and R and R′ are both methylene, and its acid addition salts and metal complexes.

11. A compound according to claim 10, wherein A′ is substituted phenylene or substituted or unsubstituted naphthylene.

12. A compound according to claim 10 or 11, wherein R and R′ are methylene.

13. A compound according to claim 10, 11 or 12, wherein Z and Y are identical.

14. A compound according to any one of claims 10 to 13, wherein the Z and Y moieties have from 9 to 20 ring members.

15. A compound according to any one of claims 10 to 14, wherein the Z and Y moieties have from 3 to 6 nitrogen atoms.

16. The compound of claim 10 which is 1,1′-[5-nitro-1,3-phenylenebis(methylene)]bis-1,4,8,11-tetraazacyclo-tetradecane.

17. The compound of claim 10 which is 1′1′-[2,4,5,6-tetrachloro-1,3-phenylenebis(methylene)]bis-1,4,8,11-tetraaza-cyclotetradecane.

18. The compound of claim 10 which is 1,1′-[2,3,5,6-tetra-fluoro-1,4-phenylenebis(methylene)]bis-1,4,8,11-tetraazacyclo-tetradecane.

19. The compound of claim 10 which is 1,1′-[1,4-naphthylene-bis(methylene)]bis-1,4,8,11-tetraazacyclo-tetradecane.

20. The compound of claim 10 which is 1,1′-[1,4-naphthlyene-bis(methylene)]bis-1,5,9,13-tetraazacyclohexadecane.

21. The compound of claim 10 which is 1,1′-[1,3-phenylenebis-(methylene)]bis-1,4,7-triazacyclododecane.

22. The compound of claim 10 which is 1,1′-[1,4-phenylene-phenylenebis(methylene)]-1,4,7-triazacyclododecane.

23. A compound according to claim 10, substantially as hereinbefore described.

24. A method for the production of a compound according to claim 10, comprising nucleophilic attack by cyclic polyamines Z′ and Y′ each being a polyamine Z or Y as defined in claim 1 and having a single unprotected ring amine nitrogen, all other ring amine nitrogens being protected, on a compound of formula II,

$$X - R - A' - R' - X \quad (II)$$

wherein R, R′ and A′ are as defined in claims 1 and 10 respectively, and

X is an active substituent which can be displaced by the unprotected amine nitrogens of polyamines Z′ and Y′,

and subsequently deprotecting the ring amine nitrogens.

25. A method according to claim 24, wherein the substitution takes place in the presence of a solvent and in the presence of a base.

26. A method according to claim 24 or 25, wherein the nitrogen atoms of the cyclic polyamines are protected by methanesulfonyl and/or 4-tolylsulfonyl and/or diethylphosphoryl.

27. A method according to claim 24, 25 or 26, wherein the deprotection is carried out in a mixture of HBr and acetic acid in the case of methanesulfonyl and 4-tolylsulfonyl protection or by HCl in THF or dioxane in the case of diethylphosphoryl protection.

28. A method according to claim 24, substantially as hereinbefore described.

IMPROVEMENTS IN CHEMICAL COMPOUNDS

Abstract of the Invention

Linked cyclic polyamines of formula

Z - R - A - R′ - Y

where Z and Y are each cyclic polyamine moieties, A is an aromatic or heteroaromatic moiety, and R and R′ are each an alkylene chain or heteratom-containing chain, show high activity against HIV, and low toxicity, in in vitro tests. Novel compounds, and pharmaceutical compositions are claimed.